REMARKS

Claims 1-37 are currently pending. Claim 38 has been withdrawn. Claims 21 has been amended to correct punctuation. No new matter has been added.

The rejection of claims 1-4, 14-31, 33, and 35-37 under 35 U.S.C. §103(a) over Gitan et al. (Genome Research, 2001, 12, 158-164) in view of Bransteitter et al. (PNAS, 2003, 100, 4102-4107) is respectfully traversed.

Gitan et al. discloses a method known as methylation specific oligonucleotide microarray. This method uses bisulphate-modified DNA as a template for PCR amplification. Bisulphite-modification results in conversion of unmethylated cytosine but not methylated cytosine into thymine within CpG islands of interest in the PCR product (see abstract). There is no disclosure in Gitan et al. of the use of an enzyme which differentially modifies methylated cytosine and unmethylated cytosine in single stranded DNA.

The deficiency of Gitan is not cured by Bransteitter. Bransteitter is broadly directed to an enzyme treatment to differentially modulate DNA comprising methylated and unmethylated cytosine. Bransteitter does not disclose measuring the presence or level of alkylated cytosine in a DNA sample. Further, Bransteitter is non-analogous art and a person of ordinary skill in the art would not have considered this reference in order to solve the problem of providing a new method for detecting the presence or level of alkylated cytosines in a sample of genomic or mitochondrial DNA.

Bransteitter describes a series of experiments which were conducted in order to elucidate the activity of the AID in B cells. Specifically, the authors investigated the contribution of the enzyme on somatic hypermutation, i.e., a high frequency of mutation that occurs in the gene segments encoding the variable regions of antibodies during the differentiation of B cells into antibody producing plasma cells. Therefore, Applicants respectfully submit that the person of skill in the relevant art to Bransteitter would be a B cell immunologist, not a person developing novel assays to measure methylation patterns.

The Office Action points to three sections of Bransteitter which allegedly teach that AID modulates the activity of single stranded DNA comprising cytosine and methylated cytosine differently, namely the abstract, Figure 4b and page 4106, column 1, paragraph 4. As a first point, Applicants submit that the abstract is completely silent on the issue of methylation, and, in fact, it concludes only that AID catalyses deamination of dC residues on single stranded DNA *in vitro* but not on double stranded DNA, RNA-DNA hybrids or RNA.

Further, the experiments described on page 4106 and Figure 4b were designed to confirm and extend the previous finding that the sole activity observed for AID was with a free nucleoside (CR) or deoxynucleoside CdR substrate, and that this activity was not reliant upon the pre-treatment of RNAses. The aim of the experiments described in this paragraph was to elucidate the need for RNAses, not the measurement of methylation patterns.

In *In re Winslow*, 151 USPQ 48 (CCPA 1966), the court states that:

Section 103 requires us to presume full knowledge by the inventors [more properly, of the person of ordinary skill in the art] of the prior art in the field of his endeavor . . . but it does not presume full knowledge by the inventor of prior art outside the field of his endeavor, i.e. of "nonanalogous" art. In that respect it only requires us to presume that the inventor would have had that ability to select and utilize knowledge from other arts reasonably pertinent to his particular problem which would be expected of a man of ordinary skill in the art to which the subject matter pertains.

Applicants submit that one of ordinary skill in the art would not have considered Bransteitter to be "reasonably pertinent" to their particular problem and, therefore, would not have identified this reference, et al. one relied upon its contents.

Further, Applicants submit that a reference putatively teaching a means by which an enzyme contributes to somatic hypermutation is NOT reasonably pertinent to the particular problem with which the present inventors were involved, namely the development of novel methods for measuring methylation.

In *In re Clay*, 966 F.2d 656, 23 USPQ2d 1058 (Fed. Cir. 1992) the court held that the prior art process references to be non-analogous to the claimed invention even though both were in the petroleum industry and both involved handling petroleum products in volumetric enclosures. The claimed invention was a method for *storing refined* petroleum products in a *man-made* storage tank. The references were to a method for *extracting crude* oil from *porous* hydrocarbon-bearing *natural underground* formations. These italicized features, the court concluded, showed a different "field of endeavor" and different "purposes" which defeat the possibility of dealing with or solving a common problem.

Applicants submit that the present situation is even more removed than that discussed in *In re Clay* (supra). In *In re Clay* the references both dealt with the same technology, namely the petroleum industry. In the present situation, the present invention is in the field (industry) of measuring methylation patterns on DNA, whereas the prior art is in the field (industry) of B cell immunology. Therefore, it is for at least these reasons that Bransteitter is non-analogous art, and can therefore not be combined with the teachings of Gitan et al. to render the present invention as allegedly obvious.

Furthermore, the Office Action fails to meet its burden in making a prima facie case of obviousness. The Office bears the initial burden of factually supporting any prima facie conclusion of obviousness. The Federal Circuit has clearly stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). Conclusory statements that both references would be combined because they are both "interested in understanding the importance of methylation pattern in biological processes…" and "one having skill in the art would like to use an enzyme." do not suffice as "articulated reasoning." As such, Applicant respectfully requests withdrawal of this rejection.

The rejection of claims 1 and 4-13 under 35 U.S.C. §103(a) over Gitan et al. (Genome Research, 2001, 12, 158-164) in view of Bransteitter et al. (PNAS, 2003, 100, 4102-4107) and

further in view of Kuhn et al. (J. Am. Chem. Soc., 2002, 124, 1097-1103) is respectfully traversed.

The combination of Gitan and Bransteitter is addressed above. The addition of Kuhn et al. does not cure the deficiencies of the combination of Gitan and Bransteitter. Kuhn et al. provides information regarding separating two strands of double stranded DNA with different means including strand displacing probes. Kuhn et al. does not, however, provide any teaching or information regarding differentially modifying alkylated cytosine and cytosine present in single stranded DNA. Accordingly, even if the skilled artisan was to combine the references, as suggested in the Office Action, they would not arrive at the current invention. As such, the combined references do not render the claimed invention obvious. Thus, Applicant respectfully requests withdrawal of this rejection.

The rejection of claims 1 and 32 under 35 U.S.C. §103(a) over Gitan et al. (Genome Research, 2001, 12, 158-164) in view of Bransteitter et al. (PNAS, 2003, 100, 4102-4107) and further in view of Opdecamp et al. (Nucleic Acids Research, 1992, 20, 171-178) is respectfully traversed.

The combination of Gitan and Bransteitter is addressed above. The addition of Opedecamp et al. does not cure the deficiencies of the combination of Gitan and Bransteitter. Opdecamp et al. teaches identification of methylated DNA by using methylation-sensitive restriction enzymes. In the claimed method the enzyme is acting on single stranded DNA. It is well understood that restriction enzymes only recognize and cleave double stranded DNA. Accordingly, none of the enzymes referred to in Opdecamp differentially modify cytosine and alkylated cytosine in the single stranded DNA. Reconsideration and withdrawal of this rejection is respectfully requested.

The rejection of claims 1 and 34 under 35 U.S.C. §103(a) over Gitan et al. (Genome Research, 2001, 12, 158-164) in view of Bransteitter et al. (PNAS, 2003, 100, 4102-4107) and further in view of Paulson et al. (J. Virol., 1999, 73, 9959-9968) is respectfully traversed.

The combination of Gitan and Bransteitter is addressed above. The addition of Paulson et al. does not cure the deficiencies of the combination of Gitan and Bransteitter. Paulson et al. uses bisulphite modified DNA which is then amplified using PCR to detect sites of methylation in the viral genome. Accordingly, the methodology of Paulson et al. is similar to the methodology of Gitan et al. discussed above. There is no disclosure in Paulson et al. for use of an enzyme which differentially modifies cytosine present in single stranded DNA.

Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this response or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

An extension of the deadline for response to the Office Action is respectfully requested pursuant to 37 C.F.R. § 1.136(a) and the appropriate fee is submitted herewith.

In the event that any fees are due, please apply any charges or credits to deposit account 50-3211.

Respectfully submitted,

Date: June 16, 2010

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